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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,361	11/30/2004	Amirul Islam	3875-033 (184750)	7510

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EXAMINER	
STAPLES, MARK	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
09/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@akerman.com

Office Action Summary	Application No.	Applicant(s)	
	10/516,361	ISLAM ET AL.	
	Examiner	Art Unit	
	MARK STAPLES	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/02/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *159-185* is/are pending in the application.

4a) Of the above claim(s) *182-185* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *159-181* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment of claims 159, 160, 162, 163, 165-171, 174, 176, 178, and 181 and the submission of new claims 182-185 in the paper filed on 08/02/2010 is acknowledged.

2. Newly submitted claims 182-185 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims recite new and distinct combinations and subcombination and distinctly new elements of ligase and others not recited in the original claims.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 182-185 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 159-181 consonant with species election of SEQ ID NOs: 19 and 25 (see Applicant Remarks filed 05/28/2009) are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections and Rejections that are Withdrawn

3. The objection to claim 171 is withdrawn in light of Applicant's amendment of the claim.

Claim Rejections Withdrawn - 35 USC § 112 Second Paragraph

4. The rejections of claims 160, 163, 165, and 167 under 35 USC § 112 Second Paragraph are withdrawn in light of Applicant's amendments which overcome the rejections.

Claim Rejections Withdrawn- 35 USC § 103(a)

5. All prior art rejections under 35 U.S.C. 103(a) are withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment. It is noted that Applicant also argues unexpected results, however those results are not unexpected in view of Chagovetz (United States publication 2002/0197611 filed Jun. 21, 2001, newly cited) who teach the labeled forward and reverse primers as claimed. Modifications of those primers as claimed are obvious from the other cited prior art as given below.

New Rejections Necessitated by Amendment

The following table is re-provided for later discussion.

Table 1 (re-provided)

100% Sequence Matches for SEQ ID Nos. 19 and 25

SEQ ID NO. 19

Application 10516361 and Search Result 20080724_093709_us-10-516-361b-19.rge.

Title: US-10-516-361B-19
Perfect score: 20
Sequence: 1 ggggtactacagcgccctga 20

RESULT 5
LEIGPAA
LOCUS LEIGPAA 3105 bp DNA linear INV 26-APR-1993
DEFINITION L.donovani.
ACCESSION M60048
VERSION M60048.1 GI:159334
KEYWORDS glycoprotein 63.
SOURCE Leishmania donovani
ORGANISM Leishmania donovani
Eukaryota; Euglenozoa; Kinetoplastida; Trypanosomatidae;
Leishmania.
REFERENCE 1 (bases 1 to 3105)
AUTHORS Webb,J.R., Button,L.L. and McMaster,W.R.
TITLE Heterogeneity of the genes encoding the major surface glycoprotein
of Leishmania donovani
JOURNAL Mol. Biochem. Parasitol. 48 (2), 173-184 (1991)
PUBMED 1762629
COMMENT Original source text: L.donovani DNA.
FEATURES Location/Qualifiers
source 1. .3105
/organism="Leishmania donovani"
/mol_type="genomic DNA"
/db_xref="taxon:5661"
gene 101. .1873
/gene="gp63"
CDS 101. .1873
/gene="gp63"
/codon_start=1
/product="glycoprotein 63"
/protein_id="AAA29244.1"
/db_xref="GI:159335"

/translation="MSVDSSSTHRHRSVAARLVRLAAAGAAVIAAVGTAAAWAHAGAV

QHRCIHDAMQARVRQSVARHHTAPGAVSAVGLSYVTLGAAPTVVRAANWGALRIAVST

EDLTDSAYHCARVGQRISTRDGRFAICTAEDILTDEKRDILVKYLIPQALQLHTERLK

VRQVQDKWKVTGMGNEICGHFKVPPAHITDGLSNTDFVMYVASVPSEGDVLAWATTCQ

VFSDGHPAVGVINIPAANIASRYDQLVTRVVTHEMAHALGFSVVFFRDARILESISNV

```
RHKDFDVPVINSSTAVAKAREQYGCGTLEYLEMEDQGGAGSAGSHIKMRNAQDELMAP

ASDAGYYSALTMAIFQDLGFYQADFSKAEEMPWGRNAGCAFLSEKCMEDGITKWPAMF

CNENEVTMRCHTGRLSLGVCGLSSSDIPLPPYWQYFTDPLLAGISAFMDYCPVVVPFG

DGSCAQRASEAGAPFKGFNVFSDAARCIDGAFRPKTTETVTNSYAGLCANVRCDTATR

TYSVQVHGGSGYANCTPGLRVELSTVSSAFEEGGYITCPPYVEVCQGNVQAAKDGGNA
                    AAGRRGPRAAATALLVAALLAVAL"
ORIGIN

  Query Match             100.0%;  Score 20;  DB 12;  Length 3105;
  Best Local Similarity   100.0%;  Pred. No. 6.2;
  Matches   20;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 GGGGTACTACAGCGCCCTGA 20
              ||||||||||||||||||||
Db       1114 GGGGTACTACAGCGCCCTGA 1133
```

SEQ ID NO. 25

From NCBI

```
LOCUS       LEIGPAA           3105 bp    DNA     linear   INV 26-APR-1993
DEFINITION  L.donovani.
ACCESSION   M60048
VERSION     M60048.1  GI:159334
KEYWORDS    glycoprotein 63.
SOURCE      Leishmania donovani
  ORGANISM  Leishmania donovani
            Eukaryota; Euglenozoa; Kinetoplastida; Trypanosomatidae;
            Leishmania.
REFERENCE   1  (bases 1 to 3105)
  AUTHORS   Webb,J.R., Button,L.L. and McMaster,W.R.
  TITLE     Heterogeneity of the genes encoding the major surface
glycoprotein
            of Leishmania donovani
  JOURNAL   Mol. Biochem. Parasitol. 48 (2), 173-184 (1991)
   PUBMED   1762629
COMMENT     Original source text: L.donovani DNA.
FEATURES             Location/Qualifiers
     source          1..3105
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                     /db_xref="taxon:5661"
     gene            101..1873
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                     /codon_start=1
                     /product="glycoprotein 63"
                     /protein_id="AAA29244.1"
                     /db_xref="GI:159335"

/translation="MSVDSSSTHRHRSVAARLVRLAAAGAAVIAAVGTAAAWAHAGAV

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EDLTDSAYHCARVGQRISTRDGRFAICTAEDILTDEKRDILVKYLIPQALQLHTERLK

VRQVQDKWKVTGMGNEICGHFKVPPAHITDGLSNTDFVMYVASVPSEGDVLAWATTCQ

VFSDGHPAVGVINIPAANIASRYDQLVTRVVTHEMAHALGFSVVFFRDARILESISNV

RHKDFDVPVINSSTAVAKAREQYGCGTLEYLEMEDQGGAGSAGSHIKMRNAQDELMAP

ASDAGYYSALTMAIFQDLGFYQADFSKAEEMPWGRNAGCAFLSEKCMEDGITKWPAMF

CNENEVTMRCHTGRLSLGVCGLSSSDIPLPPYWQYFTDPLLAGISAFMDYCPVVVPFG

DGSCAQRASEAGAPFKGFNVFSDAARCIDGAFRPKTTETVTNSYAGLCANVRCDTATR

TYSVQVHGGSGYANCTPGLRVELSTVSSAFEEGGYITCPPYVEVCQGNVQAAKDGGNA
                     AAGRRGPRAAATALLVAALLAVAL"
ORIGIN
        1 cccacacgca cgcgcacacc gccgtgcaca agccctcgcc ctcgccctcg ccgtcgccac
       61 cacaccccac tgcccacagc gcccccgcgc ctgcagagcc atgtccgtcg acagcagcag
      121 cacgcaccgg caccgcagcg tcgccgcgcg cctggtgcgc ctcgcggctg ccggcgccgc
      181 agtcatcgct gctgtcggca ccgcggccgc gtgggcacac gccggtgcgg tgcagcaccg
      241 ctgcatccac gacgcgatgc aggcacgcgt gcggcagtcg gtggcgcgcc accacacggc
      301 ccccggcgcc gtgtccgcgg tgggcctgtc gtacgttact ctcggcgccg cgcccacagt
      361 cgtgcgcgcc gcgaactggg gcgcgctgcg catcgccgtc tccaccgagg acctcaccga
      421 ctccgcctac cactgcgctc gcgtcgggca gcgtattagc acgcgcgatg gccgcttcgc
      481 catctgcacc gccgaggaca tcctcaccga cgagaagcgc gacatcctgg tcaaatacct
      541 catcccgcag gcgctgcagc tgcacacgga gcggctgaag gtgcggcagg tgcaggacaa
      601 gtggaaggtg acgggcatgg gcaacgagat ctgtggccac ttcaaggtgc cgccggcgca
      661 catcaccgat ggcctgagca acaccgactt cgtgatgtac gtcgcctccg tgccgagcga
      721 gggggatgtg ctggcgtggg ccacgacctg ccaggtgttc tctgacggcc atccagccgt
      781 gggcgtcatc aacatccccg cggcgaacat tgcgtcgcgg tacgaccagc tggtgacgcg
      841 tgtcgtcacg cacgagatgg cgcacgcgct cggcttcagc gtcgtcttct tccgagacgc
      901 ccgcatcctg gagagcattt cgaacgttcg gcacaaggac ttcgatgttc ccgtgatcaa
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     1021 ggagatggag gaccagggcg gtgcgggctc cgccgggtcg cacatcaaga tgcgcaacgc
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     1141 catcttccag gacctcggct tctaccaggc ggacttcagc aaggccgagg agatgccgtg
     1201 gggccggaac gccggctgcg ccttcctcag cgagaagtgc atggaggacg gcatcacgaa
     1261 gtggccggcg atgttctgca atgagaacga ggtgactatg cgctgccaca ccggtcgtct
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```

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1561 cgaaaccgta acaaattcgt acgccggact gtgcgccaac gtgcggtgcg acacggccac
1621 gcgcacgtac agcgtgcagg tgcacggcgg cagcggctac gccaactgca cgccgggcct
1681 cagagttgag ctgagcaccg tgagcagcgc cttcgaggag ggcggctaca tcacgtgccc
1741 gccgtacgtg gaggtgtgcc agggcaacgt gcaggctgcc aaggacggcg gcaacgccgc
1801 ggctggtcgc cgtggtccgc gcgccgcggc gacggcgctg ctggtggccg cgctgctggc
1861 cgtggcgctc tagacggtgg ataggacggg tggtgatggc gtgtcccctg ctccccccctc
1921 cctccctccc tctcgttgtc tctcggaaga gctccacgct gtcctttcat ctcctcgcct
1981 gttctacgct tgcttccgtg cgccgctgca ccgggccggt cctcgccgac cctcgcctgc
2041 cctctccccc tcctctctcc cgccacccca ccccgcttcc cgctgcgcac ggtgcctgtg
2101 cgcttggaga ggtgcagcag cgcgcgggag ctgagggagg gaggggtgt cgtgcgcggg
2161 tgcgcatgcc ttctttcact tccttatttg tcttctattt gttccctgcg acacccgcac
2221 acccccaccc gctggcggcc atccgcggca tccgcgggtg cgtgcgcggt gtgtctgcct
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3061 ccccactgcc cacagcgccc ccgcgcctgc agagccatgt ccgtc
```

```
>gb|M60048.1|LEIGPAA  L.donovani
Length=3105
 Score = 40.1 bits (20),  Expect = 8e-06
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Minus

Query  1     GTCCTGGAAGATGGCCATGG  20
             ||||||||||||||||||||
Sbjct  1153  GTCCTGGAAGATGGCCATGG  1134
```

New Claim Rejections - 35 USC § 103(a)

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 159-168, 171-176, and 178-180 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chagovetz (United States publication 2002/0197611 filed Jun. 21, 2001, newly cited), Solinas et al. (Oct. 15, 2001) and Nazarenko et al. (2000, previously cited, hereinafter referred to as Nazarenko et al. (2000)).

Regarding claims 159, 162-165, 167, 171, 176, and 178, Chagovetz teaches methods of detection and quantification of a target nucleic acid sequence and/or a nucleic acid amplification reaction using a nucleic acid amplification (entire publication) comprising the step of:

having a Molecular Energy Transfer (MET)/Fluorescent Resonance Energy Transfer (FRET) between a donor MET/FRET moiety and an acceptor MET/FRET moiety separately on at least two separate oligonucleotides and separately on twoprimers (see Figures and claims 1-19) ,

wherein the said moieties on two oligonucleotides/primers are provided in the oligonucleotides/primers for the acceptor (A) and the donor (D) is at least 1 base away from the 3' end (see Figures 7 and 8) is adapted to inhibit signal from primer dimer, and eliminate non-specific signal generation when the (MET/FRET moiety) labelled oligonucleotides are subjected to extension by a polymerase in a nucleic acid PCR amplification reaction with the target nucleic acid (see Figures and claims 1-19) ,and

wherein a MET/FRET signal is generated from donor and acceptor on amplification of said target nucleic acid sequence when the MET/FRET moieties are separated by 4-20 or 25 nucleotides in the amplification product by teaching that the donor and acceptor are separated not greater than 100 angstrom (see claim 5).

Regarding claim 159, Chagovetz teach donor labels are internal in oligonucleotides and thus suggest but do not specifically teach the donor labels are internal by at least 2 bases from the 3' end of the oligonucleotide. Chagovetz alos teach the donor acceptor are separated by minimal distance (see paragraph 0022) and thus it would have been obvious to one of ordinary skill in the art the time of the claimed invention to optimize that distance for various donor acceptor pairs.

Regarding claim 161, Chagovetz teaches a third labeled oligonucleotide (see claim 15).

Regarding claim 168, Chagovetz. teaches multiplex assays by teaching mutliple primers (see claim 15).

Regarding claim 172, Chagovetz teaches CY5™ dyes (see paragraph 0009).

Regarding claims 179 and 180, Chagovetz teaches the sequence is from a human for detection of one nucleotide mutation differences (see Example)

Regarding claims 159, 162-165, 167, 171, 176, and 178, Solinas et al. teach methods of detection and/or quantification of a target nucleic acid sequence and/or a nucleic acid amplification reaction using a nucleic acid amplification (entire article) comprising the step of:

having a Molecular Energy Transfer (MET)/Fluorescent Resonance Energy Transfer (FRET) between a donor MET/FRET moiety and an acceptor MET/FRET moiety separately on at least two separate oligonucleotides (see Figure 5),

wherein the said moieties on two oligonucleotides are provided in the oligonucleotides on a base at least 2 bases away from its 3' end is adapted to inhibit signal from primer dimer, and eliminate non-specific signal generation when the (MET/FRET moiety) labelled oligonucleotides are subjected to extension by a polymerase in a nucleic acid PCR amplification reaction with the target nucleic acid (see Figure 5B where the internal donor FAM and an internal methyl red dA acceptor/quencher are each internal by at least 2 bases and see p. 7), and

wherein a MET/FRET signal is generated from donor and acceptor on amplification of said target nucleic acid sequence when the MET/FRET moieties are separated by 4-20 or 25 nucleotides in the PCR amplification product from PCR (see Figure 5 and see 2nd paragraph on p. 8).

Regarding claim 160 and 167, Solinas et al. teach primers which are 10-40 nucleotides in length (see Table 2).

Regarding claim 172, Solinas et al. teach FAM and ROX (see legend to Table 2).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the internally labeled oligonucleotides of Chagovetz. by placing the labels at least 2 bases away from the 3' ends as suggested by Solinas et al. with a reasonable expectation of success. The motivation to do so is provided by Solinas et al. who teach that internal placement of donor and acceptor labels of primer dimer pairs is easily accomplished by labeling internal thymidines (see last sentence of the 1st paragraph on p. 7) and provides an intermolecular probe target interaction for fast and reliable detection of target nucleic acids (see last sentence of the 2nd paragraph on p. 1). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Regarding claim 159, Nazarenko et al. (2000) teach improved methods of detection and/or quantification of a nucleic acid target sequence by a nucleic acid amplification reaction (entire patent, specifically column 7 lines 14-21) with internal MET/FRET labels (see Figures 7 and 8) comprising:

(i) a first oligonucleotide sufficiently complementary to hybridize to a first nucleic acid strand of a target sequence and to act as a nucleic acid amplification primer, and a second oligonucleotide sufficiently complementary to hybridize to the complement of the

said first nucleic acid strand and to act as a nucleic acid amplification primer in an appropriate reaction mixture by teaching:

> "The invention provides a method for detecting or measuring a product of a nucleic acid amplification reaction comprising: (a) contacting a sample comprising nucleic acids with at least two oligonucleotides, a first one of said oligonucleotides comprising a sequence complementary to a preselected target sequence that may be present in said sample, and said first one and a second of said oligonucleotides being a pair of primers adapted for use in said amplification reaction . . . " (see column 13 lines 27-34),
>
> "In another embodiment, the donor moiety is located on a first oligonucleotide and the acceptor is located on a second oligonucleotide" (see column 16 lines 23-26),
>
> and teach that the donor and acceptor can be MET moieties and FRET moieties which are a type of MET moieties and teach the MET/FRET distance is 10-100 Angstrom (see column 1 lines 14-16 lines 30-56) which is within the range of 10-80 Angstrom,
>
> and teach: "The target nucleic acid can be genomic or cDNA or mRNA or synthetic, human or animal, or of a microorganism . . (see column 20 lines 3-5);

the amplification reaction mixture containing the said sample and a polymerase, where the polymerase is a DNA polymerase (see claim 95) which can be Taq polymerase (see column 25 lines 12-16), wherein the said reaction mixture is subjected to an initial denaturation followed by repeated cycles of a combination of a denaturation step and at least a selective annealing step (taught throughout the patent, see for example column 56 lines 32-38 and see Figure 5 and its description at the bottom of column 8) ,

(ii) the said first and the second oligonucleotide primers do not form any combination in absence of an amplification reaction as they are hairpin primers , wherein the improvement comprises:

(ii) the presence of a target sequence in the sample being detected with improved sensitivity and specificity of the amplification product through the generation of a signal mainly on formation of a combination of the two primers and a combination of the two labels on the two separate primers on target amplification, and illuminating the PCR amplification reaction mixture in thin walled tubes with an UV transilluminator image analysis system (see Figure 23 and its description at column 11 lines 9-15).

Regarding claim 159, Nazarenko et al. (2000) teach donor labels are internal in oligonucleotides and thus suggest but do not specifically teach the donor labels are internal by at least 2 bases from the 3' end of the oligonucleotide.

Regarding claim 162 , 166, and 167, Nazarenko et al. (2000) teach providing a third oligonucleotide labeled with a third label moiety and teach first , second, and third oligonucleotide primers by teaching "a third nucleotide sequence of 6-30 nucleotides, wherein a nucleotide within said third nucleotide sequence is *labeled with a second moiety* [noting that this is the third label of the claims as Nazaneko et al. teach that their can be a second primer with different labels as given above and where label can internal on the oligonuceltoide, see claims 1-4 and Table 5] selected from the group consisting of said donor moiety and said acceptor moiety, and said second moiety is the member of said group not labeling said first nucleotide sequence, wherein said third nucleotide sequence is sufficiently *complementary* in reverse order to said *first nucleotide sequence* for a duplex to form between said first nucleotide sequence and said third nucleotide sequence such that said first moiety and second moiety are in

sufficient proximity such that, when the donor moiety is excited and emits energy, the acceptor moiety absorbs energy emitted by the donor moiety; and (d) at the 3' end of said oligonucleotide, a fourth, single-stranded nucleotide sequence of 8-40 nucleotides that comprises at its 3' end a sequence sufficiently complementary to a preselected target sequence so as to be able to prime synthesis by a nucleic acid polymerase of a nucleotide sequence complementary to a nucleic acid strand comprising said target sequence; wherein when said duplex is not formed, said first moiety and said second moiety are separated by a distance that prevents molecular energy transfer between said first and second moiety" (emphasis by Examiner, see column 20 lines 21-66, and see Figure 6 and see column 8 lines 60-65). Furthermore, Nazarenko et al. teach that multiple primers can be used in amplification and that each primer can be labeled with different fluorophores and/or different quenchers (see Table 1 for a list of FRET pairs and see column 17 lines 46-67). Furthermore, Nazarenko et al. teach that primers may be provided in semi-nested amplification which is a type of nested amplification (see column 4 lines 9-16). Even further, Becker et al. teach a third oligonucleotide can be used to nest between FRET primers (see Real-time PCR on p. 2563 and referencing Holland et al.).

Further regarding claim 162, Chagovetz teaches as noted above and teach amplification teach:

a primer labeled near the 3' ,

an unlabeled primer,

a third labeled oligonucleotide,

where the labeled primer is incorporated into the sequence and where the labels are MET/FRET donor and acceptor and come within the MET distance on the target nucleic acid (as given above and see claim 15).

Regarding claim 168, Nazarenko et al. (2000) teach multiplexing of targets and labels (see column 36 lines 3-9).

Regarding claims 172-174, Nazarenko et al.(2000) teach donors and acceptors of fluorescein, DABCYL (see column 3 lines 3-17), and ethidium bromide (see column 10 line 30 and claim 37) which inherently is an intercalator and teach rhodamine (claim 23), carboxy fluorescein (calim 25), Malachite green (claim 40), and TEXAS RED® acceptor (claim 41).

Regarding claim 175, Nazarenko et al (2000) teach biotin and avidin (see column 19 lines 50-57). Nazarenko et al. teach adding polymerase, reaction buffer, deoxy nucleoside triphosphates (dNTPs) in addition to the effective amounts of the amplification primers to the samples, cycling the sample between at least a denaturation temperature and an elongation temperature, exciting the reaction mixture with the donor exciting radiation or light, measuring the emission of the acceptor MET moiety (see column 35 lines 46 to column 36 line 61 and see column 38 lines 16-26).

Regarding claim 179, Nazarenko et al (2000) where the target nucleic acid sequence is an amplficiation product of the infectious disease agent which is Chlamydia (see Table 3).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the MET/FRET methods of Chagovetz and Solinas et al. with the intermediary acceptor of ROX, donor of FAM, and a general acceptor/quencher which specifically can be methyl red dA is by using ethidium bromide as an intermediary acceptor as suggested by Nazarenko et al. (2000) with a reasonable expectation of success. The motivation to do so is provided by Nazarenko et al. (2000) who teach that ethidium bromide is a quencher and Solinas et al. who teach primer dimer pairs with an intermediary quencher prevents fluorescence cross talk and thus results in more specific detection of target nucleic acids (see last sentence on p. 7 continued to p. 8). Furthermore, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention to substitute ethidium bromide quencher as taught by Nazareko et al. (2000) for the quencher of Solinas et al. to arrive at the clamed invention. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

9. Claims 169, 170, and 177 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chagovetz (2001), Solinas et al. (2001), and Nazarenko et al. (2000) as applied to claim 159 above, and further in view of Andersson et al. (2001, previously cited) and Chetverin et al. (1993, previously cited).

Chagovetz, Solinas et al. and Nazarenko et al. (2000) do not specifically teach a covalent linker to a solid support but teach the other limitations of claims 169 and 170 as found above and teach high throughput/multiplex methods.

Regarding claims 169, 170, and 177, Andersson et al. teaches attachment of probes/primers to solid supports (column 11 lines 55 and 56) which can be through a covalent linking moiety (column 11 line 15) and detection through FRET (see column 10 line 22) and where solid phase can be the translucent silica or glass polymers for amplification and detection of 5' end bound target nucleic acids as further taught by Chetverin et al. (see p. 8, 3rd paragraph and claims 36, 41, and 144).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Chagovetz, Solinas et al. and Nazarenko et al. (2000) by using linkers to solid supports as suggested by Andersson et al. and Chetverin et al. with a reasonable expectation of success. The motivation to do so is provided by Andersson et al. who teach that methods using the covalently bound probes of Chetverin et al. have enhanced sensitivity (column 11 lines 20 and 21). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

10. Claims 159-168, 171-176, and 178-180 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chagovetz (United States publication 2002/0197611 filed Jun. 21, 2001, newly cited), Sato et al. (WO 1998/13524 published 2000) and Nazarenko et al. (2000, previously cited, hereinafter referred to as Nazarenko et al. (2000)).

Regarding claims 159, 162-165, 167, 171, 176, and 178, Chagovetz teaches methods of detection and quantification of a target nucleic acid sequence and/or a

nucleic acid amplification reaction using a nucleic acid amplification (entire publication) comprising the step of:

having a Molecular Energy Transfer (MET)/Fluorescent Resonance Energy Transfer (FRET) between a donor MET/FRET moiety and an acceptor MET/FRET moiety separately on at least two separate oligonucleotides and separately on twoprimers (see Figures and claims 1-19) ,

wherein the said moieties on two oligonucleotides/primers are provided in the oligonucleotides/primers for the acceptor (A) and the donor (D) is at least 1 base away from the 3' end (see Figures 7 and 8) is adapted to inhibit signal from primer dimer, and eliminate non-specific signal generation when the (MET/FRET moiety) labelled oligonucleotides are subjected to extension by a polymerase in a nucleic acid PCR amplification reaction with the target nucleic acid (see Figures and claims 1-19) ,and

wherein a MET/FRET signal is generated from donor and acceptor on amplification of said target nucleic acid sequence when the MET/FRET moieties are separated by 4-20 or 25 nucleotides in the amplification product by teaching that the donor and acceptor are separated not greater than 100 angstrom (see claim 5).

Regarding claim 159, Chagovetz teach donor labels are internal in oligonucleotides and thus suggest but do not specifically teach the donor labels are internal by at least 2 bases from the 3' end of the oligonucleotide. Chagovetz also teach the donor acceptor are separated by minimal distance (see paragraph 0022) and thus it would have been obvious to one of ordinary skill in the art the time of the claimed invention to optimize that distance for various donor acceptor pairs.

Regarding claim 161, Chagovetz teaches a third labeled oligonucleotide (see claim 15).

Regarding claim 168, Chagovetz. teaches multiplex assays by teaching mutliple primers (see claim 15).

Regarding claim 172, Chagovetz teaches CY5™ dyes (see paragraph 0009).

Regarding claims 179 and 180, Chagovetz teaches the sequence is from a human for detection of one nucleotide mutation differences (see Example)

Regarding claims 159-165, 167, 171, 176, and 178, Sato et al. teach methods of detection and/or quantification of a target nucleic acid sequence and/or a nucleic acid amplification reaction using a nucleic acid amplification (entire publication) comprising the step of:

having a Molecular Energy Transfer (MET)/Fluorescent Resonance Energy Transfer (FRET) between a donor MET/FRET moiety and an acceptor MET/FRET moiety separately on at least two separate oligonucleotides (see Figure 5),

wherein the said moieties on two oligonucleotides are provided in the oligonucleotides on a base at least 2 bases away from its 3' end by teaching both donor and acceptor are from bases 4 to 20 in the hybrid (see paragraph 0034 and Figures 1B and 1D) and any 2' position of a ribose in the oligonucleotide may be labeled (see paragraph 0041 and Table 1 and see paragraphs 0096-0117 for examples of oligonucleotides labeled internally more 2 bases from the 3' end) is adapted to inhibit signal from primer dimer, and eliminate non-specific signal generation, and

wherein a MET/FRET signal is generated from donor and acceptor on amplification of said target nucleic acid sequence when the MET/FRET moieties are separated by 4 to 20 in the hybrid (see paragraph 0034 and Figures 1B and 1D).

Regarding claim 159, Sato et al. do not specifically teach extension.

Regarding claim 161, Sato et al. teach a third oligonucleotide (see paragraph 0038 description of Figure 1F).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the internally labeled oligonucleotides of Nazarenko et al. by placing the labels at least 2 bases away from the 3' ends as suggested by Sato et al. with a reasonable expectation of success. The motivation to do so is provided by Sato et al. who teach at length that the separation distance of the donor and quencher are important and the hybridized oligonucleotides can maintain this separation distance with internal labels of donor and quencher. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Regarding claim 159, Nazarenko et al. (2000) teach improved methods of detection and/or quantification of a nucleic acid target sequence by a nucleic acid amplification reaction (entire patent, specifically column 7 lines 14-21) with internal MET/FRET labels (see Figures 7 and 8) comprising:

(i) a first oligonucleotide sufficiently complementary to hybridize to a first nucleic acid strand of a target sequence and to act as a nucleic acid amplification primer, and a second oligonucleotide sufficiently complementary to hybridize to the complement of the said first nucleic acid strand and to act as a nucleic acid amplification primer in an appropriate reaction mixture by teaching:

> "The invention provides a method for detecting or measuring a product of a nucleic acid amplification reaction comprising: (a) contacting a sample comprising nucleic acids with at least two oligonucleotides, a first one of said oligonucleotides comprising a sequence complementary to a preselected target sequence that may be present in said sample, and said first one and a second of said oligonucleotides being a pair of primers adapted for use in said amplification reaction . . . " (see column 13 lines 27-34),
>
> "In another embodiment, the donor moiety is located on a first oligonucleotide and the acceptor is located on a second oligonucleotide" (see column 16 lines 23-26),
>
> and teach that the donor and acceptor can be MET moieties and FRET moieties which are a type of MET moieties and teach the MET/FRET distance is 10-100 Angstrom (see column 1 lines 14-16 lines 30-56) which is within the range of 10-80 Angstrom,
>
> and teach: "The target nucleic acid can be genomic or cDNA or mRNA or synthetic, human or animal, or of a microorganism . . (see column 20 lines 3-5);

the amplification reaction mixture containing the said sample and a polymerase, where the polymerase is a DNA polymerase (see claim 95) which can be Taq polymerase (see column 25 lines 12-16), wherein the said reaction mixture is subjected to an initial denaturation followed by repeated cycles of a combination of a denaturation step and at least a selective annealing step (taught throughout the patent, see for example column 56 lines 32-38 and see Figure 5 and its description at the bottom of column 8) ,

(ii) the said first and the second oligonucleotide primers do not form any combination in absence of an amplification reaction as they are hairpin primers , wherein the improvement comprises:

(ii) the presence of a target sequence in the sample being detected with improved sensitivity and specificity of the amplification product through the generation of a signal mainly on formation of a combination of the two primers and a combination of the two labels on the two separate primers on target amplification, and illuminating the PCR amplification reaction mixture in thin walled tubes with an UV transilluminator image analysis system (see Figure 23 and its description at column 11 lines 9-15).

Regarding claim 159, Nazarenko et al. (2000) teach donor labels are internal in oligonucleotides and thus suggest but do not specifically teach the donor labels are internal by at least 2 bases from the 3' end of the oligonucleotide.

Regarding claim 162 , 166, and 167, Nazarenko et al. (2000) teach providing a third oligonucleotide labeled with a third label moiety and teach first , second, and third oligonucleotide primers by teaching "a third nucleotide sequence of 6-30 nucleotides, wherein a nucleotide within said third nucleotide sequence is *labeled with a second moiety* [noting that this is the third label of the claims as Nazaneko et al. teach that their can be a second primer with different labels as given above and where label can internal on the oligonuceltoide, see claims 1-4 and Table 5] selected from the group consisting of said donor moiety and said acceptor moiety, and said second moiety is the member of said group not labeling said first nucleotide sequence, wherein said third

nucleotide sequence is sufficiently *complementary* in reverse order to said *first nucleotide sequence* for a duplex to form between said first nucleotide sequence and said third nucleotide sequence such that said first moiety and second moiety are in sufficient proximity such that, when the donor moiety is excited and emits energy, the acceptor moiety absorbs energy emitted by the donor moiety; and (d) at the 3' end of said oligonucleotide, a fourth, single-stranded nucleotide sequence of 8-40 nucleotides that comprises at its 3' end a sequence sufficiently complementary to a preselected target sequence so as to be able to prime synthesis by a nucleic acid polymerase of a nucleotide sequence complementary to a nucleic acid strand comprising said target sequence; wherein when said duplex is not formed, said first moiety and said second moiety are separated by a distance that prevents molecular energy transfer between said first and second moiety" (emphasis by Examiner, see column 20 lines 21-66, and see Figure 6 and see column 8 lines 60-65). Furthermore, Nazarenko et al. teach that multiple primers can be used in amplification and that each primer can be labeled with different fluorophores and/or different quenchers (see Table 1 for a list of FRET pairs and see column 17 lines 46-67). Furthermore, Nazarenko et al. teach that primers may be provided in semi-nested amplification which is a type of nested amplification (see column 4 lines 9-16). Even further, Becker et al. teach a third oligonucleotide can be used to nest between FRET primers (see Real-time PCR on p. 2563 and referencing Holland et al.).

Further regarding claim 162, Chagovetz teaches as noted above and teach amplification teach:

a primer labeled near the 3' ,

an unlabeled primer,

a third labeled oligonucleotide,

where the labeled primer is incorporated into the sequence and where the labels are MET/FRET donor and acceptor and come within the MET distance on the target nucleic acid (as given above and see claim 15).

Regarding claims 172-174, Nazarenko et al.(2000) teach donors and acceptors of fluorescein, DABCYL (see column 3 lines 3-17), and ethidium bromide (see column 10 line 30 and claim 37) which inherently is an intercalator and teach rhodamine (claim 23), carboxy fluorescein (calim 25), Malachite green (claim 40), and TEXAS RED® acceptor (claim 41).

Regarding claim 175, Nazarenko et al.(2000) teach biotin and avidin (see column 19 lines 50-57). Nazarenko et al. teach adding polymerase, reaction buffer, deoxy nucleoside triphosphates (dNTPs) in addition to the effective amounts of the amplification primers to the samples, cycling the sample between at least a denaturation temperature and an elongation temperature, exciting the reaction mixture with the donor exciting radiation or light, measuring the emission of the acceptor MET moiety (see column 35 lines 46 to column 36 line 61 and see column 38 lines 16-26).

Regarding claim 179, Nazarenko et al. where the target nucleic acid sequence is an amplficiation product of the infectious disease agent which is Chlamydia (see Table 3).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the MET/FRET methods of Chagovetz and Sato et al. with the acceptor of ROX, donor of FAM, and a general acceptor/quencher which is ethidium bromide as suggested by Nazarenko et al. (2000) with a reasonable expectation of success. The motivation to do so is provided by Nazarenko et al. (2000) who teach that ethidium bromide is a quencher and Sato et al. who teach primer dimer pairs with donor and quencher prevents fluorescence results in more specific detection of target nucleic acids. Furthermore, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention to substitute ethidium bromide quencher as taught by Nazareko et al. (2000) for the quencher of Sato et al. or Chagovetz to arrive at the clamed invention. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

11. Claim 181 is rejected under 35 U.S.C. 103(a) as being unpatentable over (1) Chagovetz, Solinas et al. and Nazarenko et al. (2000) or (2) Chagovetz, Sato et al. and Nazarenko et al. (2000) as applied to claim 159 above, and further in view of Webb et al. (1993, previously cited) and Buck et al. (1998, previously cited).

Chagovetz, Solinas et al., Sato et al., and Nazarenko et al. (2000) teach as noted above.

With regard to claim 181, Chagovetz, Solinas et al., Sato et al., and Nazarenko et al. (2000)) disclose amplification of DNA with primers designed for amplification and detection as given above.

Chagovetz, Solinas et al., Sato et al., and Nazarenko et al. (2000) teach primers and probes in general and teach various primer and probe sequences but do not specifically teach SEQ ID NOs: 19 or 25.

Webb et al. expressly disclose the identical nucleic acid sequences presented in SEQ ID NOs: 19 and 25 of the instant disclosure in Accession no. M60048 (see Table 1 above). It is noted that the instant primer sites of SEQ ID NOs: 19 and 25 are contained within the sequence disclosed by Webb et al.

The above described references of Chagovetz, Solinas et al., Sato et al., Nazarenko et al. (2000) ,and Webb et al. do not specifically disclose the identical primer sequences of SEQ ID NOs: 19 and 25 primers, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art

compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the Accession no. M60048 and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It

is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success

Conclusion

12. No claim is free of the prior art.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-

9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 7:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark Staples/
Primary Examiner, Art Unit 1637
September 23, 2010